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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,939	09/12/2003	Frank A. Skraly	MBX 048	8379

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ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,939	SKRALY, FRANK A.	
	Examiner	Art Unit	
	Iqbal Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 16-35* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 24-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/21/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a non-provisional of provisional application of 60/410,087 filed on 9/12/2002.

The preliminary amendment filed on 2/13/2006 amending claims 1 and 24, canceling claims 13-15 and 36-38 is acknowledged. Claims 1-12, and 16-35 are at issue and are present for examination.

Applicant's election without traverse of Group III, claims 16-23, drawn to a recombinant organism expressing recombinant enzyme genes, and poly (3-hydroxyalkanoate) PHA synthetase and acyl-CoA transferase as species in the response filed on 2/13/2006 is acknowledged. Claims 1-12 and 24-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 16-23 are at issue and are present for examination.

Applicants traverse the election of species on the ground(s) that the generic claims do not recite such a multiplicity of species that an unduly extensive or burdensome search be necessary. In addition, applicants argue that the genes and gene products responsible for PHA synthesis are well known in the art, have been described in the patent literature and are reviewed in Williams and peoples, Chemtech, 26:38-44, 1996; Williams and peoples, Chem. Br. 33:29-32, 1997 and furthermore applicant argue that one ordinary skill in the art would appreciate that it could be the same PHA synthase that would act as a poly(3-hydroxyalkanoate) synthase, poly (4-hydroxyalkanoate) synthase, or poly(4-hydroxybutyrate synthase). Therefore, a search for PHA synthases would inherently include poly (3-hydroxyalkanoate) synthase, poly (4-

hydroxyalkanoate) synthase and poly (4-hydroxybutyrate) synthase and examiner would not be over-burdened. This is not found persuasive because poly(3-hydroxyalkanoate) synthase, poly (4-hydroxyalkanoate) synthase, or poly(4-hydroxybutyrate synthase) are each structurally and functionally different and distinct.

However, after further review, the examiner finds that the species of genes, which are placed as independent inventions, should be considered as species. Therefore, if the recited elected species (poly(3-hydroxyalkanoate) PHA synthetase and acyl-CoA transferase) were allowable, the examiner would rejoin the other species, as they are integral part of the present invention.

Claims 16-23 are at issue and are present for examination.

Priority

Acknowledgement is made of applicants claim for priority of provisional application 60/410,087 of 9/12/2002.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: ---A recombinant bacteria or plant over-expressing CoA-dependent alcohol dehydrogenase gene for the production of polyhydroxyalkanoate ---.

Claim Objections

Claim 18 is objected to because of the recitation "gene encoding enzymes" should be "one or more genes encoding an enzyme". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 16 and 21-23 are directed to a recombinant organism comprising and expressing a heterologous gene encoding any CoA-dependent aldehyde dehydrogenase from any source. Claim 17 recites that the said organism further comprises a gene encoding any PHA synthase and claim 18 recites that said organism further comprises one or more genes encoding enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase and acetoacetyl-CoA reductase. Claims 19 and 20 recite that the one or more genes claimed in claim 18 are either endogenous or heterologous to said organism As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately

described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification teaches the structure of only a single representative species of gene encoding CoA-dependent aldehyde dehydrogenase, three representative species of PHA synthase, single representative species of acyl-CoA transferase, single representative species of acyl-CoA synthetase, single representative species of β-ketothiolase and single representative species of acetoacetyl-CoA reductase. Moreover, the specification fails to describe any other representative species by sufficient identifying characteristics or properties other than the functionality of encoding CoA-dependent an aldehyde dehydrogenase, PHA synthase, acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase and acetoacetyl-CoA reductase. Given this lack of description of representative species encompassed by the genus of DNAs used in the said recombinant organism, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 16-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant E. coli DH5α comprising a plasmid expressing the CoA-dependent aldehyde dehydrogenase gene eutE from E. coli, does not reasonably provide enablement for any recombinant organism or any recombinant bacteria or any recombinant plant

comprising a plasmid having any CoA-dependent aldehyde dehydrogenase gene or any PHA synthase gene or any acyl-CoA transferase gene or any acyl-CoA synthetase or any β-ketothiolase or any poly(4-hydroxybutyrate) synthase and any acetoacetyl-CoA reductase from any source. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 16-23 are so broad as to encompass any recombinant organism or any recombinant bacteria or any recombinant plant comprising a plasmid having any aldehyde dehydrogenase gene (CoA-dependent), any PHA synthase gene or any poly(4-hydroxybutyrate) synthase or any acyl-CoA transferase gene or any acyl-CoA synthetase or any β-ketothiolase and any acetoacetyl-CoA reductase gene from any source. Claim 17 recites that the said organism further comprising any gene encoding any PHA synthase and claim 18 recites that the said organism further comprising genes encoding enzymes selected from the group consisting of any acyl-CoA transferase, any acyl-CoA synthetase, any β-ketothiolase and any acetoacetyl-CoA reductase and claim 19 recites that one or more genes are endogenous. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of aldehyde dehydrogenase gene (CoA-dependent), PHA synthase gene or poly(4-hydroxybutyrate) synthase or acyl-CoA transferase gene or acyl-CoA synthetase or β-ketothiolase and acetoacetyl-CoA reductase gene broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in

the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequences of only one aldehyde dehydrogenase gene (CoA-dependent), one acyl-CoA transferase gene or one acyl-CoA synthetase or one β-ketothiolase and one acetoacetyl-CoA reductase gene and three PHA synthase gene.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass any recombinant organism or any recombinant bacteria or any recombinant plant comprising a plasmid having any aldehyde dehydrogenase gene (CoA-dependent), any PHA synthase gene or any acyl-CoA transferase gene or any acyl-CoA synthetase gene or any β-ketothiolase gene and any acetoacetyl-CoA reductase gene because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting polypeptide activity; (B) the general tolerance of polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any aldehyde dehydrogenase or any acyl-CoA transferase or any acyl-CoA synthetase or any β-ketothiolase and any acetoacetyl-CoA reductase residues with

an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any recombinant organism or any recombinant bacteria or any recombinant plant comprising a plasmid having any CoA-dependent aldehyde dehydrogenase gene or any acyl-CoA transferase gene or any acyl-CoA synthetase gene or any β-ketothiolase gene and any acetoacetyl-CoA reductase gene. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any recombinant organism or any recombinant bacteria or any recombinant plant comprising a plasmid having any said genes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Toth et al. (Appl Environ Microbiol. 1999 Nov; 65(11): 4973-80, see IDS). Toth et al. disclose the

isolation, cloning and sequencing of an ald gene, encoding a coenzyme A-acylating aldehyde dehydrogenase, from Clostridium acetobutylicum. Toth et al. also disclose the transforming bacteria with the cloned said coenzyme A-acylating aldehyde dehydrogenase gene in a vector. Toth et al. further disclose that the ald gene encodes a polypeptide of 468 amino acid residues with a calculated M(r) of 51, 353. Therefore, Toth et al. anticipate claims 16 and 22 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-20 and 22-23 are rejected under 35 U.S.C. 103(a) as being obvious over Skraly et al. (US Patent 6,329,183 B1, publication 12/11/2001, see IDS) in view of Toth et al. (Appl Environ Microbiol. 1999 Nov; 65(11): 4973-80, see IDS). Skraly et al. disclose a method for producing polyhydroxyalkanoates comprising a recombinant bacteria or a plant comprising and expressing acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and polyhydroxyalkanoate synthase (PHA synthase), and additionally glycerol-3-phosphate dehydrogenase and glycerol-3-phosphatase in presence of polyols (a kind alcohol) which can be converted into 3-hydroxypropionate or 3-hydroxyvalerate monomers by enzymes expressed by organisms, and culturing the organisms under conditions wherein 3-hydroxypropionate or 3-hydroxyvalerate is polymerized to form polyhydroxyalkanoates. Skraly et al. also disclose that the organisms are genetically engineered with plasmids encoding one or more of the additional enzymes. Skraly et al. further disclose that the organisms are genetically engineered with genes encoding an enzyme aldehyde dehydrogenase for the production of polyhydroxyalkanoates. Skraly et al. do not disclose the expression of a CoA-dependent aldehyde dehydrogenase in the recombinant organism. Toth et al. disclose the isolation, cloning and sequencing of an ald gene, encoding a coenzyme A-acylating aldehyde dehydrogenase, from Clostridium acetobutylicum. Toth et al. also disclose that the ald gene encodes a polypeptide of 468 amino acid residues with a calculated M(r) of 51, 353.

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to use the CoA-dependent aldehyde dehydrogenase gene of Toth et al. to transform the

recombinant organism comprising acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and polyhydroxyalkanoate synthase (PHA synthase), to produce a recombinant strain expressing CoA-dependent aldehyde dehydrogenase for the enhanced production of polyhydroxyalkanoates (PHAs) as disclosed by Skraly et al.

One of ordinary skill in the art would have been motivated to use CoA-dependent aldehyde dehydrogenase gene in order to convert propionaldehyde to propionyl-CoA efficiently wherein propionyl-CoA and acetyl-CoA would be converted to 3-hydroxyvaleryl-CoA by using beta-ketothiolase for the efficient production of PHAs, which is industrially useful as polymer.

One of ordinary skill in the art would have a reasonable expectation of success because use of heterologous gene for over-expression in a recombinant organism to produce acylating coenzyme A from corresponding aldehyde are customary and widely used in the art.

Claims 16-20, 21 and 22-23 are rejected under 35 U.S.C. 103(a) as being obvious over Skraly et al. (US Patent 6,329,183 B1, publication 12/11/2001, see IDS) in view of Goodlove et al. (Gene 1989 Dec 21; 85(1): 209-14). Skraly et al. disclose a method for producing polyhydroxyalkanoates comprising a recombinant bacteria or a plant comprising and expressing acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and polyhydroxyalkanoate synthase (PHA synthase), and additionally glycerol-3-phosphate dehydrogenase and glycerol-3-phosphatase in presence of polyols (a kind alcohol) which can be converted into 3-hydroxypropionate or 3-hydroxyvalerate monomers by enzymes expressed by organisms, and culturing the organisms under conditions wherein 3-hydroxypropionate or 3-hydroxyvalerate is polymerized to form polyhydroxyalkanoates. Skraly et al. also disclose that

the organisms are genetically engineered with plasmids encoding one or more of the additional enzymes. Skraly et al. further disclose that the organisms are genetically engineered with genes encoding an enzyme aldehyde dehydrogenase for the production of polyhydroxyalkanoates. Skraly et al. do not disclose the expression of CoA-dependent aldehyde dehydrogenase into the recombinant organism. Goodlove et al. disclose the isolation, cloning and sequencing of a 6-kb fragment of DNA from Escherichia coli comprising both ADH (alcohol dehydrogenase) and coenzyme-A-linked acetaldehyde dehydrogenase (ACDH) activities were encoded by the plasmid, pHIL8, wherein adhE gene was identified as an open reading frame of 891 codons encoding an Mr 96,008 protein (minus the initiating methionine).

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to use the CoA-dependent aldehyde dehydrogenase gene of Goodlove et al. from E. coli to transform the recombinant organism comprising acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and polyhydroxyalkanoate synthase (PHA synthase), to produce a recombinant strain expressing CoA-dependent aldehyde dehydrogenase for the enhanced production of polyhydroxyalkanoates (PHAs) as disclosed by Skraly et al.

One of ordinary skill in the art would have been motivated to use CoA-dependent aldehyde dehydrogenase gene in order to convert propionaldehyde to propionyl-CoA efficiently wherein propionyl-CoA and acetyl-CoA would converted to 3-hydroxyvaleryl-CoA by using beta-ketothiolase for the efficient production of PHAs, which is industrially useful as polymer.

One of ordinary skill in the art would have a reasonable expectation of success because use of heterologous gene for over-expression in a recombinant organism to produce acylating coenzyme A from corresponding aldehyde are customary and widely used in the art.

Conclusion

Status of the claims:

Claims 16-23 are pending.

Claims 16-23 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

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